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ЦИТОКИНЫ КАК ПРЕДИКТОРЫ КИШЕЧНОЙ МЕТАПЛАЗИИ ЖЕЛУДКА

Матвеева Л.В.

ФГБОУ ВО «Национальный исследовательский Мордовский государственный университет имени Н.П. Огарёва», г. Саранск, Республика Мордовия, Россия

Резюме. В основе заболеваний гастродуоденальной зоны лежит воспалительный процесс на фоне изменений мукозальной микробиоты. Хронизация воспаления слизистой оболочки желудка развивается и поддерживается путем индукции *Helicobacter pylori* и другими микроорганизмами секреции эпителиоцитами и иммуноцитами как провоспалительных, так и противовоспалительных цитокинов. В условиях дисбиоза и иммунной дисрегуляции желудочный эпителий может уподобляться тонкокишечному или толстокишечному. Целью работы стало определение диагностической и прогностической ценности цитокинов при кишечной метаплазии желудочного эпителия.

При информированном согласии 204 больных с обострением хронического гастрита, язвенной болезни желудка, полипозом желудка и 40 здоровых добровольцев проводили забор гастробиоптатов при эзофагогастродуоденоскопии (для гистологического и микробиологического исследования), 5 мл венозной крови с отделением сыворотки (для иммуноферментного анализа). Сывороточные уровни цитокинов исследовали твердофазным иммуноферментным методом. При статистической обработке результатов вычисляли чувствительность, специфичность показателей, уравнения логистической регрессии, строили характеристические кривые с определением индекса согласованности модели по площади под кривыми (AUC).

При гистологическом исследовании гастробиоптатов признаки тонкокишечной метаплазии были обнаружены у 61 (29,90%) больного, толстокишечной – у 40 (19,61%), отсутствовали у клинически здоровых добровольцев. Наибольшая чувствительность при тонкокишечной метаплазии отмечалась у интерлейкина (IL)-6, IL-4, эритропоэтина (EPO), туморнекротизирующего фактора (TNF)α, IL-18, фактора роста эндотелия сосудов (VEGF), интерферона (IFN)α, при толстокишечной метаплазии – у рецепторного антагониста IL-1β (IL-1ra), IL-8, EPO, IL-18, моноцитарного хемоаттрактантного протеина (MCP)-1, VEGF, IFNα, IL-1β, IL-6, IL-17. Общим признаком стало увеличение IL-6, EPO, IL-18, VEGF, IFNα, косвенно с учетом функциональной активности цитокинов указывающее на микробную контаминацию желудка, тканевую гипоксию с активацией ангиогенеза, подтверждая этапность кишечной метаплазии в канцерогенезе желудка. Наибольшая специфичность при тонкокишечной метаплазии отмечалась у IL-1β, IL-1ra, IL-8, IL-17, IL-2, IL-10, при толстокишечной метаплазии – у IL-18, IFNα, IL-4, MCP-1, VEGF. При тонкокишечной метаплазии интервал AUC больше 0,7 определялся у IL-2, больше 0,65 – у VEGF, при толстокишечной метаплазии больше 0,91 – у IL-18, VEGF, MCP-1, IFNα, и имел уровень значимости < 0,001. Полученные прогностические модели развития кишечной метаплазии желудка, судя по AUC, имели очень хорошее (табл. 2, формула 1) и отличное качество (табл. 2, 3, формулы 2-11), что подтверждалось высоким процентом верно классифицированных признаков метаплазии.

Адрес для переписки:
Матвеева Любовь Васильевна
ФГБОУ ВО «Национальный исследовательский Мордовский государственный университет имени Н.П. Огарёва»
430032, Россия, Республика Мордовия, г. Саранск, ул. Ульянова, 26.
Тел.: 8 (8342) 35-25-16.
Факс: 8 (8342) 32-19-83.
E-mail: MatveevaLjubov1@mail.ru

Address for correspondence:
Matveeva Lyubov V.
National Research Mordovia State University
430032, Russian Federation, Republic of Mordovia, Saransk, Ulyanov str., 26.
Phone: 7 (8342) 35-25-16.
Fax: 7 (8342) 32-19-83.
E-mail: MatveevaLjubov1@mail.ru

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Определение сывороточных цитокинов при кишечной метаплазии желудочного эпителия является диагностически и прогностически ценным, следует использовать для ранней диагностики предраковых состояний желудка как изолированно (IL-2, VEGF), так и в комбинации показателей согласно рассчитанным уравнениям логистической регрессии.

Ключевые слова: интерлейкин, интерферон, моноцитарный хемотаксический протеин, Helicobacter pylori, кишечная метаплазия, желудочный эпителий, диагностическая ценность

CYTOKINES AS PREDICTORS OF INTESTINAL METAPLASIA OF STOMACH

Matveeva L.V.

National Research Mordovia State University, Saransk, Republic of Mordovia, Russian Federation

Abstract. An inflammatory process accompanied by the changes in mucosal microbiota is underlying the gastroduodenal diseases. Chronic inflammation of gastric mucosa is developed and supported by secretion of pro-inflammatory and anti-inflammatory cytokines by epithelial cells and immune cells induced by *Helicobacter pylori* and other microorganisms. Under the conditions of dysbiosis and immune dysregulation, gastric epithelial layer becomes like intestinal or colonic epithelium. The aim of this work was to determine diagnostic and prognostic value of cytokines in intestinal metaplasia of gastric epithelium.

204 patients with exacerbation of chronic gastritis, gastric ulcer, gastric polyposis and 40 healthy volunteers were included into the study, under their informed consent. The gastric biopsies were sampled by means of esophagogastroduodenoscopy (for histological and microbiological examination), along with drawing 5 ml of venous blood with serum separation (for enzyme immunoassay). Serum cytokine levels were studied by solid-phase enzyme immunoassay. In statistical evaluation of the results, we have calculated sensitivity, specificity of indexes, logistic regression equations, characteristic curves were built with the definition of the index of consistency of the model by the area under the curves (AUC).

Histological examination of gastric biopsies showed features of intestinal metaplasia in 61 patients (29.90%), colonic metaplasia was found in 40 cases (19.61%), being absent in healthy volunteers. The greatest sensitivity of intestinal metaplasia was observed for plasma levels of interleukin (IL)-6, IL-4, erythropoietin (EPO), tumor necrosis factor (TNF)α, IL-18, vascular endothelial growth factor (VEGF), interferon (IFN)α levels; in colonic metaplasia, for receptor antagonist IL-1β (IL-1ra), IL-8, EPO, IL-18, monocyte chemoattractant protein (MCP)-1, VEGF, IFNα, IL-1β, IL-6, IL-17. An increase in IL-6, EPO, IL-18, VEGF, IFNα were also common, thus indicative for changed functional activity of cytokines due to microbial contamination of gastric mucosa, tissue hypoxia with activation of angiogenesis, confirming a transition of intestinal metaplasia to gastric carcinogenesis. The greatest specificity in intestinal metaplasia was observed for IL-1β, IL-1ra, IL-8, IL-17, IL-2, IL-10; in colonic metaplasia, for IL-18, IFNα, IL-4, MCP-1, VEGF. In the intestinal metaplasia, the AUC interval was higher than 0.7 for IL-2, higher than 0.65, in VEG; in colonic metaplasia > 0.91, for IL-18, VEGF, MCP-1, IFNα, having a significance level of < 0.001. The obtained prognostic models of intestinal metaplasia of gastric epithelium, according to the AUC index, had very good (Table 2, formula 1) and excellent quality (Table 2, 3, formula 2-11), confirmed by a high percent of cases which were correctly classified of metaplasia.

Determination of serum cytokines in intestinal metaplasia of gastric epithelium is of diagnostic and prognostic value, and should be used for early diagnosis of precancerous conditions of the gastric mucosa, both as single indexes (IL-2, VEGF), and combined indicators, according to the calculated logistic regression equations.

Keywords: interleukin, interferon, monocyte chemotactic protein, Helicobacter pylori, intestinal metaplasia, gastric epithelium, diagnostic value

Introduction

At the heart of the diseases of the gastroduodenal zone there is an inflammatory process against the background of changes in the mucosal microbiota [1, 4]. The chronic inflammation of the gastric mucosa developed and supported by induction of Helicobacter pylori and other microorganisms of secretion of epithelial cells and immune cells as pro-inflammatory and anti-inflammatory cytokines [2-5]. In conditions of dysbiosis and immune dysregulation gastric

epithelium is like intestinal or colonic – metaplasia. Given the high prevalence and mortality of gastric cancer, the study of cytokine profile in intestinal metaplasia of the gastric as a precancerous change in the gastric mucosa is very relevant.

The aim of the work was to determine the diagnostic and prognostic value of cytokines in intestinal metaplasia of gastric epithelium.

Materials and methods

With the informed consent of 204 patients with exacerbation of chronic gastritis, gastric ulcer, gastric polyposis and 40 healthy volunteers, the sampling of gastrobiopaths was carried out with esophagogastroduodenoscopy (for histological and microbiological examination), 5 ml of venous blood with serum separation (for enzyme immunoassay).

Serum cytokine levels interleukin (IL)-1β, IL-2, IL-4, IL-6, IL-8, IL-10, IL-17, IL-18, receptor antagonist IL-1β (IL-1ra), interferon (IFN)α, IFNγ, tumor necrosis factor (TNF)α, monocyte chemoattractants protein (MCP)-1, granulocyte-macrophage colony stimulating factor (GM-CSF), erythropoietin (EPO), vascular endothelial growth factor (VEGF) were studied by solid-phase enzyme immunoassay with the use of reagent kits of CC "Vector-Best" (Russia).

Statistical processing of the results was performed on a computer using programs Microsoft Excel 7.0, MedCalc Version 18.11. Calculate the arithmetic mean, the error of the arithmetic average, the significance of the differences in groups according to Student's criterion, sensitivity, specificity of indicators, logistic regression equations, characteristic curves were built with the definition of the index of consistency of the model by the area under the curves (AUC), use methods Backward and Stepwise. The results were considered reliable at the significance level (P) < 0.05.

Results and discussion

Changes in the gastric microbiota and serum cytokine levels in the examined patients were described earlier [1-3].

Histological examination of gastrobiopsiej signs of intestinal metaplasia was detected in 61 (29.90%) patients, colonic – in 40 (19.61%), were absent in healthy volunteers.

The diagnostic value of cytokine determination in gastric metaplasia is presented in Table 1. Prognostic value of cytokines in intestinal metaplasia of the gastric described in Table 2, in the colonic metaplasia of the gastric – in Table 3.

The greatest sensitivity in intestinal metaplasia was observed in IL-6 (10 pg/ml), IL-4 (2-2.5 pg/ml), EPO (> 8.8 mMe/ml), TNFα (> 6.2 pg/ml), IL-18 (> 315 pg/ml), VEGF (> 246-260 pg/ml), IFNα (> 8 pg/ml). In colonic metaplasia, greater sensitivity was determined in IL-1ra (> 190 pg/ml), IL-8 (> 10 pg/ml), EPO (> 12,8 mMe/ml), IL-18 (> 395 pg/ml), MCP-1 (> 238 pg/ml), VEGF (> 350 pg/ml), IFNα (> 16 pg/ml), IL-1β (> 8 pg/ml), IL-6 (> 6 pg/ml), IL-17 (> 8 pg/ml). Common signs were an increase in IL-6, EPO, IL-18, VEGF, IFNα, indirectly taking into account the functional activity of cytokines indicating microbial contamination of the gastric, tissue hypoxia with the activation of angiogenesis, confirming the staging of intestinal metaplasia in gastric carcinogenesis.

The greatest specificity in intestinal metaplasia was observed in IL-1β (5 pg/ml), IL-1ra (126 pg/ml), IL-8 (7-10 pg/ml), IL-17 (> 14 pg/ml), IL-2 (> 15 pg/ml), IL-10 (13-14 pg/ml), in colonic metaplasia – in IL-18, IFNα, IL-4 (> 5 pg/ml), MCP-1, VEGF.

It should be noted that in case of intestinal metaplasia, the significant level of IFNγ (15-17 pg/ml) exceeded the upper limit of normal values, as well as the number of IFNα, TNFα, VEGF, IL-2, IL-17, in case of colonic metaplasia was > 17 pg/ml.

In intestinal metaplasia, the AUC interval was greater than 0.7 in IL-2, greater than 0.65 in VEGF, in colonic metaplasia greater than 0.91 in IL-18, VEGF, MCP-1, IFNα, and had a significance level of < 0.001.

The obtained prognostic models of intestinal metaplasia of the gastric, according to AUC, had very good (Table 2, formula 1) and excellent quality (Table 2, 3, formula 2-11), which was confirmed by a high percent of cases correctly classified of metaplasia.

Logistic regression equations for intestinal metaplasia were successfully tested to predict colonic metaplasia, with partial changes in the formulas taking into account the sensitivity and specificity of cytokines to improve the quality of prognostic models.

The diagnostic value of IL-8 (formulas 2-4, 6, 11) determines the contribution of neutrophilic granulocytes to the development of intestinal metaplasia of the gastric.

The combination of IL-2, IL-10 and IL-17 in formulas 3, 4, 5 indirectly indicates the simultaneous participation of different subpopulations of T-lymphocytes-helpers in the pathomorphosis of the gastric mucosa, which can be caused by dysbiosis gastroduodenal zone, determined in patients [1].

Determination of serum cytokines in intestinal metaplasia of the gastric epithelium is diagnostically and prognostically valuable, should be used for early diagnosis of precancerous conditions of the gastric both in isolation (IL-2, VEGF), and in a combination of indicators according to the calculated logistic regression equations.

TABLE 1. DIAGNOSTIC VALUE OF CYTOKINES IN INTESTINAL METAPLASIA OF THE GASTRIC

Variable	IL-1β	IL-1ra	IL-2	IL-4	IL-6	IL-8	IL-10	IL-17	IL-18	IFNα	IFNγ	TNFα	MCP-1	GM-CSF	EPO	VEGF
intestinal metaplasia of gastric epithelium																
Sensitivity, %	24.6	29.5	72.1	96.7	100	41.0	54.1	1.6	86.9	80.3	50.8	90.2	11.5	77.0	91.8	83.6
Specificity, %	96.5	91.6	74.8	42.0	20.3	88.1	71.3	86.0	50.3	42.7	69.2	27.3	62.9	43.4	30.1	55.2
AUC*	0.593	0.602	0.737	0.612	0.563	0.562	0.630	0.510	0.615	0.537	0.591	0.539	0.506	0.555	0.553	0.652
95% CI**	0.523-0.661	0.532-0.670	0.671-0.796	0.541-0.679	0.492-0.632	0.491-0.631	0.560-0.697	0.439-0.581	0.545-0.683	0.466-0.607	0.520-0.659	0.468-0.609	0.436-0.577	0.484-0.625	0.482-0.622	0.582-0.717
P***	0.0408	0.0246	< 0,001	0.0033	0.1452	0.2186	0.0026	0.809	0.0023	0.3649	0.0285	0.3499	0.8729	0.1713	0.2027	< 0.001
colonic metaplasia of gastric epithelium																
Sensitivity, %	90	100	67.5	75.0	90.0	100	82.5	90	97.5	92.5	72.5	87.5	95.0	95.0	100	95.0
Specificity, %	53	55.5	73.8	84.1	69.5	34.1	40.9	68.9	84.1	81.7	71.3	75.6	81.7	70.7	76.8	79.9
AUC	0.770	0.812	0.636	0.814	0.857	0.607	0.549	0.852	0.962	0.915	0.798	0.891	0.920	0.869	0.879	0.924
95% CI	0.706-0.826	0.751-0.863	0.566-0.702	0.753-0.865	0.812-0.910	0.536-0.675	0.478-0.619	0.796-0.898	0.926-0.984	0.869-0.950	0.736-0.851	0.839-0.930	0.873-0.953	0.815-0.912	0.826-0.921	0.879-0.957
P	< 0.001	< 0.001	0.0101	< 0.001	< 0.001	0.0306	0.2802	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001

Note. * AUC, Area under the ROC Curve; ** CI, Confidence interval; *** P, Significance level.

TABLE 2. PROGNOSTIC VALUE OF CYTOKINES IN INTESTINAL METAPLASIA OF THE GASTRIC

Dependent	Logistic regression equation	Chi-squared	P	Se*	Sp**	Percent of cases correctly classified	AUC	95% CI
Intestinal metaplasia of gastric epithelium	logit (p) = -2.957+0.210×IL-2+0.009×IL-18+(-0.283×IFNγ) (1)	65.624	< 0.0001	40.98%	90.91%	75.98%	0.823	0.763-0.873
	logit (p) = -8.939+1.121×GM-CSF+(-2.237×IL-6)+0.304×IL-8+ +(-0.401×IL-17)+0.072×IL-18+(-0.467×IFNγ) (2)	111.875	< 0.0001	68.85%	89.51%	83.33%	0.916	0.870-0.950
	logit (p) = -30.532+(-0.096×IL-1ra)+1.117×IL-2+1.510×IL-8+ +2.004×IL-10+ +(-0.649×IL-17)+(-0.997×IFNγ)+0.866×TNFα (3)	157.966	< 0.0001	75.41%	91.61%	86.76%	0.958	0.920-0.981
	logit (p) = -42.424+(-0.061×MCP-1)+(-0.144×IL-1ra)+ +1.198×IL-2+1.925×IL-8+1.689×IL-10+(-0.884×IL-17)+ +0.081×IL-18+(-0.950×IFNγ)+1.112×TNFα (4)	179.155	< 0.0001	85.25%	95.10%	92.16%	0.977	0.946-0.993

Note. *Se, Sensitivity; **Sp, Specificity.

TABLE 3. PROGNOSTIC VALUE OF CYTOKINES IN COLONIC METAPLASIA OF THE GASTRIC

Dependent	Logistic regression equation	Chi-squared	P	Se	Sp	Percent of cases correctly classified	AUC	95% CI
Colonic metaplasia of gastric epithelium	logit (p) = -17.624+0.167×IL-2+0.289×IL-10+ +0.253×IL-17+0.696×TNFα (5)	104.382	< 0.0001	60.00%	96.34%	89.22%	0.942	0.901-0.970
	logit (p) = -10.558+0.972×GM-CSF+(-0.202×IL-8)+ +0.015×VEGF+0.014×IL-1ra (6)	107.082	< 0.0001	67.50%	96.34%	90.69%	0.954	0.916-0.979
	logit (p) = -25.969+0.051×IL-18+0.197×IFNα (7)	136.609	< 0.0001	77.50%	95.73%	92.16%	0.974	0.941–0.991
	logit (p) = -18.184 +0.038×MCP-1+(-2.555×IL-1β)+ +1.832×IL-6+0.405×IL-17+0.309×IFNα+0.499×IFNγ (8)	145.388	< 0.0001	90.00%	96.95%	95.59%	0.982	0.953- 0.995
	logit (p) = -34.099+0.209×IL-2+0.062×IL-18+0.197×IFNα (9)	147.588	< 0.0001	80.00%	97.56%	94.12%	0.983	0.954-0.996
	logit (p) = -71.673+0.587×IL-2+1.447×IL-4+0.578×IL-10+ +0.081×IL-18+1.050×TNFα (10)	163.738	< 0.0001	87.50%	98.17%	96.08%	0.991	0.967-0.999
	logit (p) = -63.861+(-0.340×IL-8)+0.122×IL-18+0.974×IFNγ (11)	163.710	< 0.0001	95.00%	98.78%	98.04%	0.993	0.969-0.999

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Автор:

Матвеева Л.В. *— к.м.н., доцент, доцент кафедры иммунологии, микробиологии и вирусологии ФГБОУ ВО «Национальный исследовательский Мордовский государственный университет имени Н.П. Огарёва», г. Саранск, Республика Мордовия, Россия*

Author:

Matveeva L.V., *PhD (Medicine), Associate Professor, Department of Immunology, Microbiology and Virology, National Research Mordovia State University, Saransk, Republic of Mordovia, Russian Federation*

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